1. Scientific Abstract

Rheumatoid arthritis (RA) is a chronic, progressive disease thought to be of autoimmune ori Although RA has systemic components the major pathologies occur in the joints, which suffer both inflammation and tissue destruction. These lead to loss of function and severe impediment, both economically and in terms of quality of life. Furthermore, patients with chronic severe RA have a shortened life expectancy. The prevalence of RA in the USA increases with age, affecting 5% of women aged 65 and older. It remains incurable and, in many cases, responds poorly to treatment. For many patients, the surgical removal of the diseased joint and its replacement by a prosthesis remains the only recourse.

In view of these severe deficiencies in the present treatment of RA, we have suggested a nov therapeutic strategy based upon the delivery of anti-arthritic genes to the synovial lining of joints. Expression of these genes leads to intraarticular production of their cognate proteins which, in the c of secreted proteins, are released into the joint. Thus the joint now becomes the site of synthesis of own anti-arthritic proteins. Not only does this obviate the problem of delivering therapeutic protein to joints, but also it minimizes exposure of non-target tissues and thus reduces side-effects.

Using the rabbit knee as a model, we have developed an *ex vivo* method for delivering genes joints. A surgical, partial synovectomy is performed and the type B, fibroblastic synoviocytes culture *in vitro*. A replication defective retrovirus, MFG, carrying the gene(s) of interest is used to transduc these cells. After confirming high *in vitro* expression of the transgene, the cells are autografted back the knee joint by intraarticular injection. The injected cells recolonize the synovium and contir produce the transgene product for several weeks. We have performed extensive studies with a encoding the human interleukin-1 receptor antagonist protein (IRAP) which has anti-arthritic potential; a phase II clinical trial using IRAP protein has recently been completed. Both human and animal data show that even very high levels of IRAP are completely non-toxic. Use of a MFG-IRAI vector in rabbits in conjunction with the *ex vivo* method alluded to above, results in the intraarticular accumulation of several ng per knee of biologically active human IRAP, which blocks the intraarticul pathologies that normally follow injection of interleukin-1. Preliminary data further suggest that delivery of the IRAP gene to synovium also inhibits the development of antigen-induced arthritis in rabbits. The *ex vivo* delivery method does not alter any of a battery of serum chemistries and hematological values that we have monitored in rabbits. Furthermore, we have not been able to detect any migration of the transplanted cells away from the knee joint into which they were injected

In view of these highly encouraging data, we are now proposing a clinical trial in which the IRAP gene will be introduced into human, rheumatoid metacarpal phalangeal (MCP) joints by an analogous *ex vivo* approach. As this is the first time that a gene will have been transferred to a hum joint, the overriding priority is that of safety. Because of this, several safety features are built into th study. The most compelling of these is that the gene will be introduced into MCP joints one week prior to their surgical removal during scheduled joint replacement surgery. However, as further security, a herpes simplex thymidine kinase gene will be co-transduced into the target cells, thus rendering them sensitive to ganciclovir. In this context it is also worth pointing out that extensive clinical tests of IRAP protein have found it to be devoid of toxicity.

Tissue recovered at the time of joint replacement surgery will be analyzed for the presence a expression of the transferred genes, and for evidence of a biological response to IRAP. Patients will undergo a rigorous, lifelong follow-up.